

*DRUG DISCRIMINATION UNDER CONCURRENT
VARIABLE-RATIO VARIABLE-RATIO SCHEDULES*

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Pigeons were trained to discriminate 5 mg/kg pentobarbital from saline under concurrent variable-ratio (VR) VR schedules, in which responses on the pentobarbital-biased lever were reinforced under the VR schedule with the smaller response requirements when pentobarbital was given before the session, and responses on the saline-biased key were reinforced under the VR schedule with the larger response requirements. When saline was administered before the session, the reinforcement contingencies associated with the two response keys were reversed. When responding stabilized under concurrent VR 20 VR 30, concurrent VR 10 VR 40, or concurrent VR 5 VR 50 schedules, pigeons responded almost exclusively on the key on which fewer responses were required to produce the reinforcer. When other doses of pentobarbital and other drugs were substituted for the training dose, low doses of all drugs produced responding on the saline-biased key. Higher doses of pentobarbital and chlordiazepoxide produced responding only on the pentobarbital-biased key, whereas higher doses of ethanol and phencyclidine produced responding only on this key less often. *d*-Amphetamine produced responding primarily on the saline-biased key. When drugs generalized to pentobarbital, the shape of the generalization curve under concurrent VR VR schedules was more often graded than quantal in shape. Thus, drug discrimination can be established under concurrent VR VR schedules, but the shapes of drug-discrimination dose–response curves under concurrent VR VR schedules more closely resemble those seen under interval schedules than those seen under fixed-ratio schedules. Graded dose–response curves under concurrent VR VR schedules may relate to probability matching and difficulty in discriminating differences in reinforcement frequency.

Key words: drug discrimination, concurrent variable-ratio schedules, concurrent fixed-ratio schedules, pentobarbital, dose–response curves, key peck, pigeons

Most drug-discrimination research has concentrated on similarities and differences in the drugs that are used as discriminative stimuli. The conditions under which drugs are established and maintained as discriminative stimuli have received much less attention. One of the most important of these conditions is the schedule of reinforcement. Our research has focused on the determination of how reinforcement contingencies influence the shape of dose–response curves when other drugs are substituted for the training drug in drug-discrimination experiments. Specifically, we have addressed the question of whether drug-discrimination responses occur as quantal units or continuous variables under different reinforcement schedules. Our experimental approach has been to vary the reinforcement schedule systematically to de-

termine whether graded or quantal dose–response curves are produced in stimulus generalization tests.

Although the influence of the schedule maintaining responding in drug discrimination may seem to be an esoteric question, it is fundamental to our understanding of stimulus generalization. As Bickel and Etzel (1985) have pointed out, a quantal generalization gradient implies that a stimulus functions as a unit that is either present or absent, whereas a graded generalization gradient suggests a proportional relation between stimulus intensity and response strength. Quantal generalization gradients, however, may sometimes appear to be continuous due to artifacts of averaging all-or-nothing responding over time or across subjects. For this reason, mean dose–response curves averaged across animals, or even across sessions, can be misleading.

In drug-discrimination experiments, subjects usually are trained to make one response in the presence of a given dose of a training drug and a different response in its absence. Subsequently, generalization gradi-

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ents are determined by varying some dimension of the discriminative stimulus, which in drug-discrimination experiments is the dose of the training drug. Under these conditions, most drug-discrimination generalization gradients, at least in individual animals, have been quantal in form (Colpaert, 1991). In the great majority of experiments on drug discrimination, however, fixed-ratio (FR) schedules of reinforcement have been used to maintain responding (Colpaert, 1987), and it has been suggested that the quantal nature of drug-discrimination responding has been imposed by the strict correlation between training conditions and the reinforcement of responding on only one of the levers under an FR schedule (Colpaert, 1986, 1987).

We have attempted to determine the role of the reinforcement schedule in shaping the drug-discrimination generalization gradient by studying drug discrimination under various schedules of reinforcement. The general finding has been that drug-discrimination generalization gradients are quantal when responding is maintained under FR schedules and are graded when responding is maintained under fixed-interval (FI) and variable-interval (VI) schedules of reinforcement. These effects occur under simple FI schedules (Massey, McMillan, & Wessinger, 1992), simple FR schedules (Colpaert, 1987; Massey *et al.*, 1992), VI schedules (Gouvier, Akins, & Trapold, 1984), second-order FR schedules (McMillan, Cole-Fullenwider, Hardwick, & Wenger, 1982), multiple FR FI schedules (McMillan & Hardwick, 1996; Snodgrass & McMillan, 1991), concurrent FR FR schedules (McMillan & Li, 1999a), concurrent FI FI schedules (McMillan & Li, 2000; McMillan, Li, & Hardwick, 1997), and concurrent VI VI schedules (Snodgrass & McMillan, 1996).

Conspicuous for their absence in this list of schedules are concurrent variable-ratio (VR) VR schedules. If responding under VR schedules is similar to responding under FR schedules, it would be anticipated that drug-discrimination generalization gradients determined under concurrent VR VR schedules would generate quantal dose-response curves, as has been shown to occur with concurrent FR FR schedules (McMillan & Li, 1999a). Indeed, in experiments that did not

involve drug discrimination, Herrnstein and Loveland (1975) and MacDonall (1988) have observed near-exclusive preference for the smaller of a pair of VR schedules in a concurrent VR VR schedule when the VR components are independent of each other. However, there is reason to believe that quantal responding does not always occur under VR schedules in drug-discrimination experiments. Holloway and Gauvin (1989) trained rats to discriminate 32 mg/kg caffeine from saline under a VR schedule of reinforcement and found that graded responding occurred in individual subjects as responding shifted from the saline key to the drug key as a function of increasing doses of caffeine. In the current experiments, we studied pentobarbital discrimination in pigeons maintained under several concurrent VR VR schedules to determine if the generalization gradient for pentobarbital and other drugs was quantal (responding shifted from responding on the saline-biased key to the pentobarbital-biased key without distributing responses across both keys at intermediate doses), as would be predicted from the findings of Herrnstein and Loveland (1975), or if responding would be distributed across both keys, as Holloway and Gauvin (1989) observed with drug discriminations under simple VR schedules.

We selected several concurrent VR VR schedules for investigation, including concurrent VR 5 VR 50, concurrent VR 10 VR 40, and concurrent VR 20 VR 30. The concurrent VR 10 VR 40 schedule was chosen for the initial schedule because we have used similar schedule values to maintain drug discrimination under concurrent FR FR schedules (McMillan & Li, 1999a). When we did not find the results that we expected under this schedule, the other two concurrent schedules were studied. These other schedule values were chosen because under the concurrent VR 5 VR 50 schedule, the ratio of responses required to produce the reinforcer under the two components of the schedule is 10:1, a value that should favor a preponderance of responding on the response key associated with the VR 5 schedule component. In contrast, under the concurrent VR 20 VR 30 this ratio is only 1.5:1, which might result in a more even distribution of responses across the two keys. The drugs chosen for the stimulus gen-

eralization determinations were the same as those that we have used in most of our previous experiments.

METHOD

Subjects

Five male White Carneau pigeons, weighing between 414 and 522 g at 80% of their free-feeding weights, were used as subjects for the experiment. They were maintained at these weights by food earned during experimental sessions and by supplemental feeding immediately after the sessions. The birds were experimentally naive at the beginning of these experiments. They were maintained in a colony room in which temperature and humidity were controlled. Lights were on in the colony room from 7:00 a.m. to 7:00 p.m. Water and grit were freely available in the home cages, but not in the test cages.

Apparatus

Test sessions were conducted in a Gerbrands pigeon chamber (Model G-5610) enclosed in a Gerbrands sound- and light-attenuating cubicle (Model G-7211). On the front panel of the cage, three Gerbrands response keys (Model 7410) were mounted 7 cm apart, 20 cm above the grid floor. A force of 15 g was required to operate each key. Keys could be transilluminated with various colored lights, but the center key was not used in these experiments and it remained dark at all times. During these experiments, the left key was transilluminated with a green light and the right key with a red light for Pigeons 386, 388, and 390. The key colors were reversed for Pigeons 387 and 389. The reinforcer was 4-s access to mixed grain, presented by a food hopper through an opening (6 cm square) located 2 cm above the grid floor centered below the keys. Two 28-VDC lights illuminated the food hopper when it was operated. A 28-VDC houselight mounted on the front left corner of the top panel illuminated the chamber when schedule contingencies were in effect. Experiments were controlled and data recorded by a Gateway 2000 microcomputer through a Microcomputer Interface II (Med Associates, Inc.) using software developed in our laboratory.

Procedure

The training of pigeons to be used in experiments on drug discrimination under concurrent schedules has been described in detail previously (Snodgrass & McMillan, 1996). Briefly, they were trained to peck the two lighted side keys on the response panel by autoshaping. After the pigeons had earned 50 reinforcers for responding on each key with only one key lighted, both keys were lighted and the schedule was changed to concurrent VR 2 VR 8. During alternating sessions, 5 mg/kg pentobarbital or saline was administered 10 min before the session. If pentobarbital was administered before the session, responding on the left key was reinforced under the VR 2 component and responding on the right key was reinforced under the VR 8 component. If saline was administered before the session, the reinforcement schedules were reversed on the two keys. Over several sessions, the sizes of the VR components were increased to their final values. Training sessions continued until 44 reinforcers had been delivered or until 2,400 s had elapsed, whichever occurred first. Pigeons were maintained under each concurrent schedule until there were no increasing or decreasing trends in the ratio of responses on the two keys over six consecutive training sessions. Hereafter, the key on which responses were reinforced under the VR schedule component with the lower VR requirement after pentobarbital administration will be referred to as the pentobarbital-biased key, and the key on which responses were reinforced under the schedule with the lowest VR requirement after saline administration will be referred to as the saline-biased key.

After responding stabilized, dose-response curves for pentobarbital and other drugs were determined during the next several months, after which the schedule was changed to a new concurrent VR VR schedule and training continued under the new schedule until performance again stabilized (about 25 training sessions); then the effects of the drugs were redetermined. This process continued until the effects of drugs on performance under all three concurrent VR VR schedules had been determined. All pigeons were trained under the concurrent VR 10 VR 40 first. After completion of the dose-re-

sponse curves under concurrent VR 10 VR 40, Pigeons 386 and 387 were switched to a concurrent VR 20 VR 30 schedule and Pigeons 388, 389, and 390 were switched to a concurrent VR 5 VR 50 schedule. After completion of the dose-response curves with responding maintained under these schedules, the schedules were reversed for the two groups of pigeons, so that all pigeons were exposed to all three concurrent VR VR schedules.

The effects of pentobarbital, *d*-amphetamine, chlordiazepoxide, ethanol, and phencyclidine on responding under the concurrent VR 10 VR 40 schedule were studied in that order, and the doses of each drug were given in a mixed order. After responding stabilized under the second concurrent schedule to which the birds were exposed, the order of drug exposure was changed to pentobarbital, phencyclidine, chlordiazepoxide, *d*-amphetamine, and ethanol. After responding stabilized under the final concurrent schedule to which the pigeons were exposed, the order of drug exposure was changed to pentobarbital, phencyclidine, *d*-amphetamine, chlordiazepoxide, and ethanol. After responding stabilized under a given schedule, test drugs were given on Tuesdays and Fridays. All dose-response curves were based on single observations in each pigeon. Additional training sessions were conducted on Mondays, Wednesdays, and Thursdays.

Drugs

Injections were administered into the breast muscle 10 min before the 40-min session in a volume of 0.1 ml/100 g of body weight, with the exception of ethanol, which was administered into the proventriculus by a gavage needle 15 min before the session. The drugs studied were sodium pentobarbital (Sigma Chemical Co., St. Louis, MO), *d*-amphetamine hydrochloride (Sigma Chemical Co.), chlordiazepoxide hydrochloride (kindly supplied by Hoffmann La Roche, Nutley, NJ), and phencyclidine hydrochloride (kindly supplied by NIDA, Rockville, MD). Drugs were dissolved in physiologic saline and doses were calculated as the salts, except for ethanol, which was obtained from the University Hospital as a 100% solution and diluted to a 10% (wt/vol) solution with tap water.

Data Analysis

The number of responses made on each key and the number of reinforcers produced by responses on each key were recorded and reported as percentages of total responses or total reinforcers. Data from single observations in individual animals that were obtained by varying the dose of each drug were plotted as a percentage of responses on the pentobarbital-biased key for graphic analysis. Overall rates of responding were calculated, and the number of changes from responding on one key to responding on the other (changeovers; COs) were recorded for each pigeon and were compared with means during training sessions with saline and 5 mg/kg pentobarbital.

Defining what is a quantal dose-response curve and what is a graded dose-response curve is somewhat arbitrary. As is commonly done in drug-discrimination research, subjects were considered to have made the saline-biased response if less than 20% of responses occurred on the pentobarbital-biased key after a drug administration. They were considered to have made the pentobarbital-biased response if more than 80% of responses occurred on the pentobarbital-biased key after a drug administration. Individual dose-response curves were considered to be quantal if no points on the dose-response curve were between 20% and 80% on the pentobarbital-biased key. Dose-response curves were considered to be graded if at least one point on the dose-response curve was between 20% and 80% of responses on the pentobarbital-biased key. The frequency with which quantal and graded dose-response curves were produced under different concurrent VR VR schedules and under different orders of exposure to these schedules was tested for statistical significance by chi-square.

RESULTS

Table 1 shows performance of individual pigeons for the last six training sessions after saline administration and the last six sessions after pentobarbital administration during sessions conducted before drug-substitution tests were initiated in pigeons trained under the concurrent VR VR schedules. Stimulus

Table 1

Mean and standard deviation (in parentheses) of the percentage of total responses on the saline-biased key and the pentobarbital-biased key, percentage of total reinforcers delivered following responses on these keys, overall response rate (responses per second) and changeovers (CO) during six saline and six pentobarbital training sessions for individual animals maintained under each concurrent schedule.

Schedule	Bird	Saline-training sessions % saline key				Pentobarbital-training sessions % pentobarbital key			
		Responses	Reinforcers	Rate	CO	Responses	Reinforcers	Rate	CO
Concurrent VR 20 VR 30	386	98 (4)	99 (2)	1.54 (0.23)	2.6 (2.5)	97 (6)	98 (5)	1.79 (0.07)	0.3 (0.8)
	387	95 (13)	96 (10)	1.91 (0.04)	0.1 (0.4)	97 (3)	97 (3)	2.13 (0.03)	0.9 (0.4)
	388	100 (0)	100 (0)	2.02 (0.15)	0.0 (0)	94 (4)	95 (3)	1.82 (0.04)	2.6 (2.5)
	389	96 (4)	97 (6)	2.05 (0.10)	0.4 (0.8)	100 (0)	99 (1)	2.16 (0.08)	0.3 (0.5)
	390	100 (0)	100 (0)	1.86 (0.11)	0.1 (0.4)	95 (10)	100 (0)	1.79 (0.28)	0.1 (0.4)
Concurrent VR 10 VR 40	386	96 (4)	98 (2)	1.42 (0.07)	1.0 (1)	100 (0)	100 (0)	1.40 (0.04)	0.0 (0)
	387	99 (1)	99 (1)	1.40 (0.03)	0.3 (0.7)	96 (4)	98 (1)	1.60 (0.04)	1.0 (0.5)
	388	100 (0)	100 (0)	1.52 (0.17)	0.1 (0.3)	90 (17)	95 (7)	1.42 (0.17)	2.1 (2.7)
	389	97 (6)	99 (2)	1.59 (0.08)	0.4 (1)	98 (6)	97 (2)	1.64 (0.06)	1.0 (0)
	390	100 (0)	100 (0)	1.42 (0.13)	0.7 (2)	98 (4)	99 (2)	1.42 (0.04)	0.4 (0.7)
Concurrent VR 5 VR 50	386	99 (2)	100 (0)	0.92 (0.03)	0.1 (0.4)	99 (2)	99 (1)	0.83 (0.11)	0.1 (0.4)
	387	92 (7)	97 (2)	1.10 (0.04)	0.7 (0.5)	100 (0)	100 (0)	0.92 (0.02)	0.7 (0.5)
	388	95 (2)	97 (1)	0.87 (0.04)	0.9 (0.4)	100 (0)	100 (0)	0.84 (0.05)	0.9 (0.4)
	389	97 (3)	98 (1)	1.04 (0.08)	1.4 (1.9)	98 (2)	99 (1)	0.96 (0.05)	1.4 (1.9)
	390	100 (0)	100 (0)	0.91 (0.03)	0.0 (0)	100 (0)	100 (0)	0.88 (0.05)	0.0 (0)

control by the presence or absence of pentobarbital was strong under all three concurrent schedules. After administration of saline, the pigeons averaged 98%, 98%, and 97% of their responses on the saline-biased key under the concurrent VR 20 VR 30, concurrent VR 10 VR 40, and concurrent VR 5 VR 50 schedules, respectively. After administration of pentobarbital, the percentages of responses on the pentobarbital-biased key were 97%, 96%, and 99% for these same three concurrent schedules. The percentage of responses on each key was closely approximated by the percentage of reinforcers delivered for responding on that key, as would be expected under a ratio schedule. Thus, stimulus control did not differ depending on whether saline or pentobarbital was administered, or on the values of the concurrent schedule. The number of COs was low for all pigeons, averaging less than one per training session after both saline and pentobarbital under all three concurrent schedules. Rates of responding were similar after saline and pentobarbital administration; however, there were differences in rates of responding that depended on the schedule. The highest baseline rates of responding were observed under the concurrent VR 20 VR 30 schedule (1.88

responses per second, 0.07 *SEM*, after saline and 1.94 responses per second, 0.17 *SEM*, after pentobarbital). Overall rates of responding were slightly lower under the concurrent VR 10 VR 40 schedule (1.47 responses per second, 0.07 *SEM*, after saline and 1.50 responses per second 0.10 *SEM*, after pentobarbital) and were much lower under the concurrent VR 5 VR 50 schedule (0.97 responses per second 0.09 *SEM*, after saline and 0.89 responses per second, 0.05 *SEM*, after pentobarbital).

Figure 1 shows the dose-response curves for the effects of increasing doses of pentobarbital on responding under each of the three concurrent schedules for individual pigeons. In general, as the dose of pentobarbital increased, responding moved from the saline-biased key to the pentobarbital-biased key. After the 10 mg/kg dose, all pigeons responded almost exclusively on the pentobarbital key under all three concurrent schedules. Both quantal and graded dose-response curves were observed in individual pigeons. Graded dose-response curves occurred for Pigeons 386, 388, and 389 under the concurrent VR 20 VR 30 schedule; Pigeons 386, 387, and 390 under the concurrent VR 10 VR 40 schedule; and Pigeons 386,

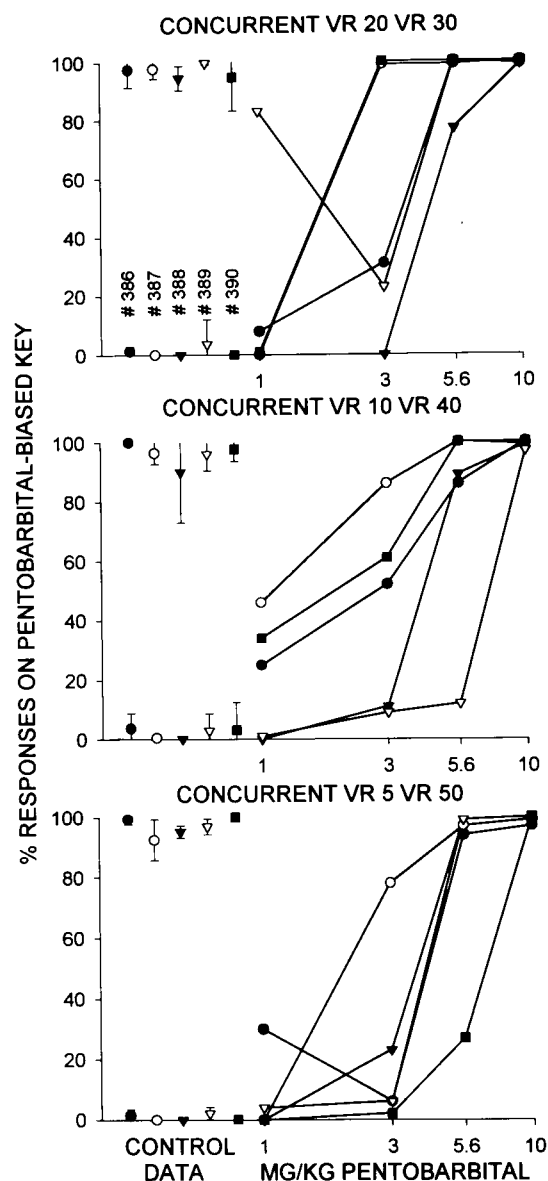


Fig. 1. Drug-discrimination generalization gradients for pentobarbital under concurrent VR 20 VR 30 (top), concurrent VR 10 VR 40 (middle), and concurrent VR 5 VR 50 (bottom). Abscissa: milligrams per kilogram dose on a log scale. Ordinate: percentage of responses on pentobarbital-biased key. Symbols and brackets at CONTROL DATA show means and standard deviations for six training sessions after responding stabilized. The top set of brackets and symbols is for training sessions after pentobarbital was administered, and the lower set of brackets and symbols is for training sessions after saline was administered. If no brackets are shown, standard deviations are smaller than the symbol. Symbols for dose-response curves represent single observations in individual pigeons. Filled circles, Pigeon 386; open circles, Pigeon 387; filled triangles, Pigeon 388; open triangles, Pigeon 389; filled squares, Pigeon 390.

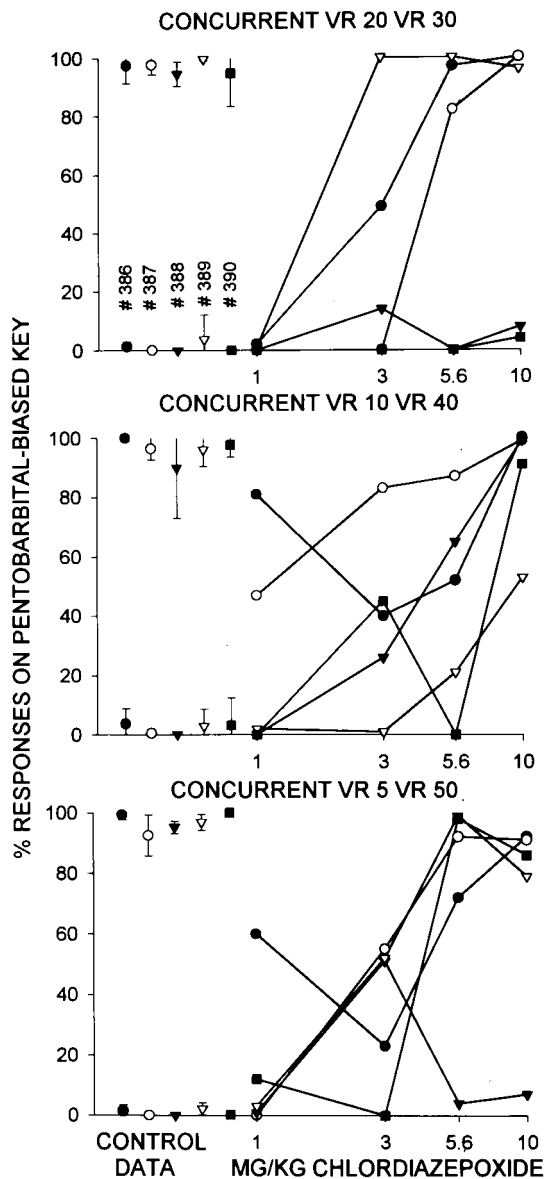


Fig. 2. Drug-discrimination generalization gradients for chlordiazepoxide under concurrent VR 20 VR 30 (top), concurrent VR 10 VR 40 (middle), and concurrent VR 5 VR 50 (bottom). Details as in Figure 1.

387, 388, and 390 under the concurrent VR 5 VR 50 schedule.

Figure 2 shows dose-response curves for the effects of chlordiazepoxide as a discriminative stimulus under each of the concurrent schedules. Under the concurrent VR 20 VR 30 schedule, only 3 pigeons (386, 387, and

389) responded predominantly on the pentobarbital-biased key after high doses of chlordiazepoxide. The other 2 responded largely on the saline-biased key. Only the data from Pigeon 386 met the criterion for a graded dose-response curve. Under the concurrent VR 10 VR 40 schedule, all pigeons except 389 responded predominantly on the pentobarbital-biased key after high doses of chlordiazepoxide, and even this pigeon made about half of its responses on the pentobarbital-biased key after 10 mg/kg chlordiazepoxide. The dose-response curves for every pigeon met the criterion for being graded, although some of the curves showed irregular reversals in the effects of some doses. Under the concurrent VR 5 VR 50 schedule, all pigeons except 388 responded predominantly on the pentobarbital-biased key after high doses of chlordiazepoxide, and all pigeons except 389 exhibited graded dose-response curves. Thus, the pentobarbital stimulus generalized to higher doses of chlordiazepoxide in most pigeons under most schedules, and the shape of the dose-response curves was more often graded than quantal.

Figure 3 shows the dose-response curves for ethanol as a discriminative stimulus under the three concurrent schedules. Under concurrent VR 20 VR 30, only Pigeons 386 and 389 responded on the pentobarbital-biased key after ethanol. The dose-response curve was graded only for Pigeon 386. Under concurrent VR 10 VR 40, only Pigeon 388 failed to respond predominantly on the pentobarbital-biased key after some dose of ethanol, although for Pigeon 390 there was a dosage reversal of effect between 1,000 and 1,800 mg/kg. Only the dose-response curves for Pigeons 386 and 387 were graded. Under concurrent VR 5 VR 50, only with Pigeon 390 was responding confined to the pentobarbital key after high doses of ethanol. To the extent that differential responding occurred with Pigeons 386, 389, and 390, dose-response curves were graded. With Pigeons 387 and 388, responding was confined largely to the saline-biased key.

Figure 4 shows the effects of phencyclidine as a discriminative stimulus under the concurrent schedules. Under concurrent VR 20 VR 30, 4 of the pigeons (386, 387, 389, and 390) responded predominantly on the pentobarbital-biased key after higher

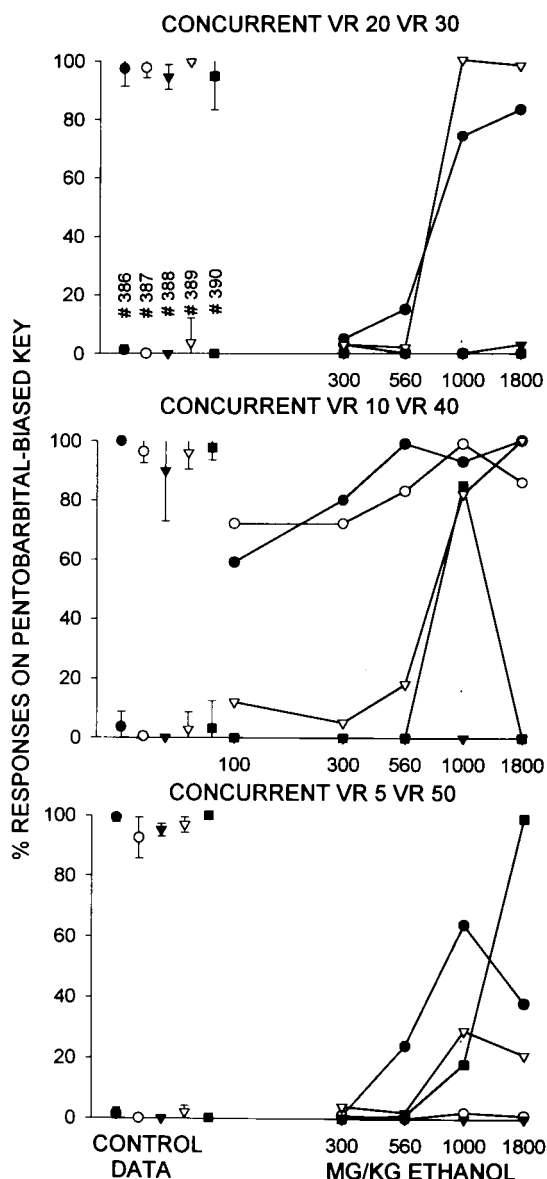


Fig. 3. Drug-discrimination generalization gradients for ethanol under concurrent VR 20 VR 30 (top), concurrent VR 10 VR 40 (middle), and concurrent VR 5 VR 50 (bottom). Details as in Figure 1.

doses of phencyclidine. The dose-response curves under this schedule met the criterion for quantal dose-response curves for 2 of these pigeons (389 and 390). Pigeon 388 responded only on the saline key until a dose was reached that eliminated responding. Under concurrent VR 10 VR 40, the

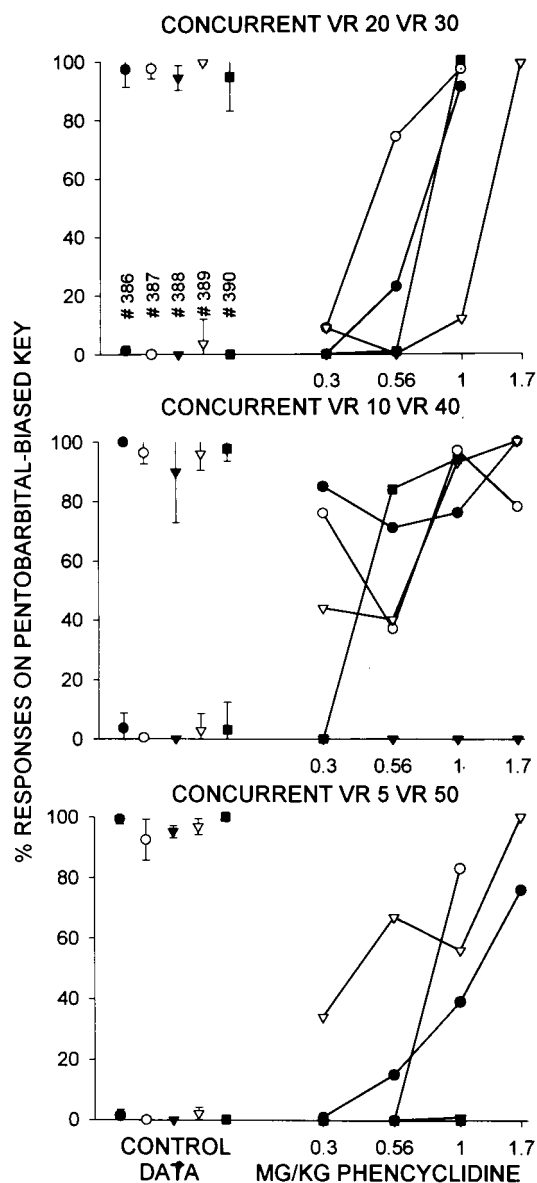


Fig. 4. Drug-discrimination generalization gradients for phencyclidine under concurrent VR 20 VR 30 (top), concurrent VR 10 VR 40 (middle), and concurrent VR 5 VR 50 (bottom). Details as in Figure 1.

results were similar, with the same 4 pigeons responding predominantly on the pentobarbital-biased key after phencyclidine and Pigeon 388 responding only on the saline key. The dose-response curves met the criterion for being graded for all of these pigeons except Pigeon 390. Under concur-

rent VR 5 VR 50, more than 80% of the responses occurred on the pentobarbital-biased key after phencyclidine in 2 pigeons (387 and 389), and Pigeon 386 approached this level. The other 2 pigeons responded only on the saline key at doses that did not eliminate responding. The dose-response curve for phencyclidine was graded in 2 of the 3 pigeons (386 and 389) that emitted a substantial amount of responding on the pentobarbital-biased key, and was quantal in the 3rd (387).

Figure 5 shows the effects of *d*-amphetamine as a discriminative stimulus under the three concurrent schedules. Under concurrent VR 20 VR 30, none of the pigeons responded predominantly on the pentobarbital-biased key, although Pigeons 386, 389, and perhaps 387 met the criterion for graded responding across the two keys after some doses. Under concurrent VR 10 VR 40, similar effects were observed, with considerable responding occurring on both keys for Pigeons 386, 387, and to a lesser extent, 390. Responding by the other pigeons was confined to the saline-biased key. Under concurrent VR 5 VR 50, responding was generally confined to the saline key, except that for Pigeon 386 responding occurred on both keys, especially after the highest dose. Under all three schedules, these curves with intermediate effects were sometimes characterized by irregular dose-response curves.

To determine if there were differences among schedules in the shapes of the dose-response curves that were generated under the different concurrent VR VR schedules, a chi-square analysis was conducted across all drugs using only the dose-response curves that met criteria for full generalization to the training drug. The frequency of graded and quantal dose-response curves did not differ significantly across the three concurrent VR VR schedules. Similarly, chi-square tests were conducted to determine if the order of exposure to the concurrent VR 20 VR 30 and the concurrent VR 5 VR 50 schedules influenced the frequency of graded and quantal dose-response curves under these schedules. Again, the results of these tests were not statistically significant.

Table 2 shows the effects of each of the test drugs on overall rates of responding. Rates of responding increased after each test

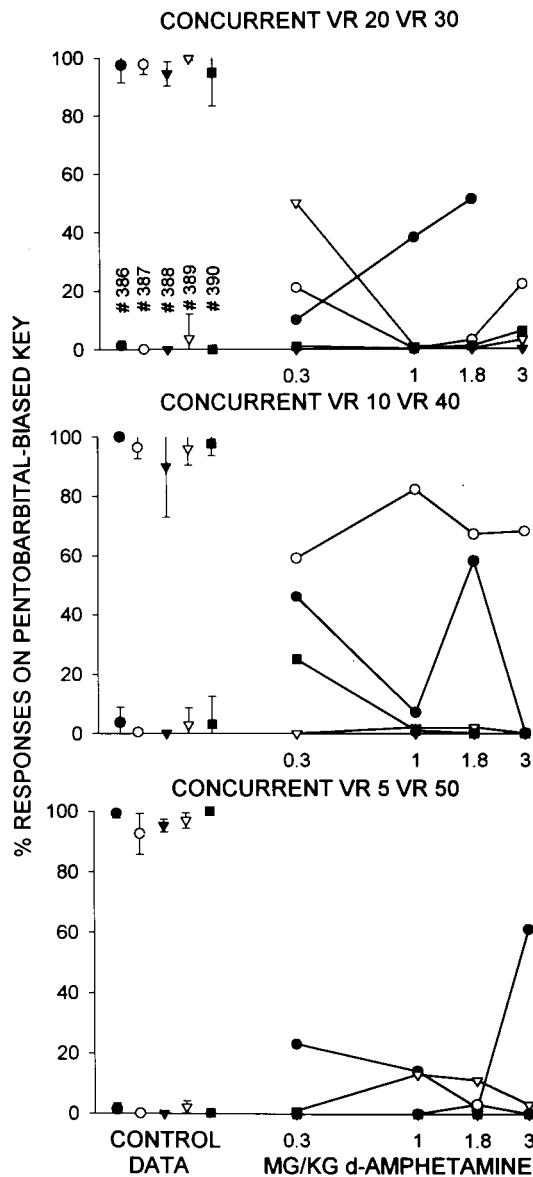


Fig. 5. Drug-discrimination generalization gradients for *d*-amphetamine under concurrent VR 20 VR 30 (top), concurrent VR 10 VR 40 (middle), and concurrent VR 5 VR 50 (bottom). Details as in Figure 1.

drug (relative to saline control sessions) for sessions under concurrent VR 5 VR 50. Under concurrent VR 10 VR 40, pentobarbital had little effect on rates of responding at the doses studied. Low doses of ethanol increased rates of responding under this schedule, but the highest dose decreased response rates. High doses of other drugs de-

Table 2

Effects of drugs on rates of responding (responses per second) under the three concurrent VR VR schedules of reinforcement. Each value represents a mean from single observations in 5 pigeons. ↓ indicates that rates were more than two standard deviations below the control mean on saline-training days. ↑ indicates that the rates were more than two standard deviations above the control mean on saline-training days.

Drug	Mg/kg	Concurrent reinforcement schedule			
		VR 20 VR 30	VR 10 VR 40	VR 5 VR 50	
Pentobarbital	1	1.79	1.50	1.96↑	
	3	2.08	1.42	1.96↑	
	5.6	1.92	1.47	2.04↑	
	10	1.89	1.47	1.87↑	
Chlordiazepoxide	1	1.75	1.55	1.82↑	
	3	1.80	1.35	1.88↑	
	5.6	1.56	1.30↓	1.82↑	
	10	1.36↓	1.42	1.22↑	
Ethanol	100	NT	1.78↑	NT	
	300	1.62	1.68↑	1.5↑	
	560	1.46↓	1.47	1.36↑	
	1,000	1.21↓	1.70	1.39↑	
	1,800	1.32↓	1.09↓	1.13	
Phencyclidine	0.3	1.85	1.59	1.95↑	
	0.56	1.74	1.54	1.83↑	
	1.0	1.26↓	1.05↓	1.01	
	1.8	0.35↓	0.53↓	1.07	
<i>d</i> -Amphetamine	0.3	1.70	1.32	1.77↑	
	1.0	1.65	1.19↓	1.68↑	
	1.8	1.48↓	1.27↓	1.55↑	
	3.0	0.94↓	1.12↓	1.28↑	
	5.6	NA	0.11↓	NT	

Note. NT = dose not tested.

creased overall rates of responding under concurrent VR 10 VR 40. Under concurrent VR 20 VR 30, high doses of all drugs except pentobarbital decreased rates of responding. The rate decreases after phencyclidine were marked compared to those of the other drugs.

DISCUSSION

The presence or absence of the training dose of pentobarbital precisely controlled the location of responding under concurrent VR VR schedules of reinforcement after responding had stabilized. Averaged across pentobarbital and saline training conditions, across the three concurrent VR VR schedules, and across individual pigeons, 98.5% (1.5% *SEM*) of responses occurred on the key with the

lower ratio requirement (Table 1). Thus, the location of responding came under the control of both the drug condition and the VR response requirement. We had anticipated that as the difference between the size of the VR components decreased, more responding would occur on the key with the higher ratio value than would occur with larger differences in the size of the VR components, but this was not the case. The distribution of responses across the two keys appeared to be independent of the differences in the VR values across the range of values studied in this experiment. Other investigators also have observed exclusive responding on the manipulandum associated with the lower ratio value under concurrent VR VR schedules in experiments that did not involve drug discriminations (Herrnstein & Loveland, 1975; MacDonall, 1988).

The major reason for conducting the present experiment was to determine the shape of the drug-discrimination generalization gradients under concurrent VR VR schedules. In a long series of experiments, we have been building a case that interval schedules generate graded dose-response curves, whereas ratio schedules generate quantal dose-response curves (see the introduction); however, all of our previous drug-discrimination experiments with ratio schedules had been conducted with some type of FR schedule (Massey *et al.*, 1992; McMillan & Hardwick, 1996; McMillan & Li, 1999a). Observations by Holloway and Gauvin (1989) had suggested that drug-discrimination generalization gradients under VR schedules might not have the same shape as those under FR schedules. This observation was confirmed in the present experiments, in that the majority of generalization gradients for those drugs that generalized completely to the training dose of pentobarbital generated graded rather than quantal dose-response curves under concurrent VR VR schedules. Chi-square tests suggested that there was no difference among the three schedules of reinforcement in the frequency with which graded and quantal dose-response curves were generated across drugs, nor were there statistically significant differences in the frequency of graded and quantal dose-response curves relating to the order of exposure to the schedules, as has

sometimes been reported for other reinforcement schedules (McMillan & Li, 1999b).

Because previous studies were consistent in showing graded dose-response curves under interval schedules and quantal dose-response curves under ratio schedules, it seemed possible that the shape of the curves depended on whether the schedule was a ratio or an interval schedule. In a previous experiment with concurrent FR 10 FR 40 schedules, pigeons trained to discriminate 5 mg/kg pentobarbital from saline exhibited quantal dose-response curves for pentobarbital and other drugs that generalize to pentobarbital (McMillan & Li, 1999a). The ratio schedule values in that study were identical to the concurrent VR 10 VR 40 schedules in the present study, yet under the concurrent FR FR schedule almost all of the dose-response curves were quantal, whereas under the concurrent VR VR schedule in the present study most were graded. The much more frequent occurrence of graded dose-response curves under the concurrent VR VR schedule than under the concurrent FR FR schedule suggests that factors other than ratio or interval scheduling of the delivery of the reinforcer play a role in the determination of the shape of the generalization dose-response curves.

A possible explanation for the differences in the shapes of the dose-response curves under concurrent VR VR schedules and concurrent FR FR schedules may be differences in the discriminability of reinforcer rates under VR and FR schedules. Under some conditions, probability matching can occur under concurrent ratio schedules, whereby the animal matches the ratio of alternative responses to the probability of reinforcement for each alternative, even though a higher reinforcement rate would occur if the animal responded exclusively on the manipulandum with the higher reinforcement rate (Bitterman, 1965). Clearly, probability matching did not occur under baseline conditions in the present study, because responding was confined almost exclusively to the alternative with the highest reinforcement rate under the concurrent VR VR schedule. Nevertheless, it is possible, under the influence of a drug dose that is not the training dose or training drug, that probability matching may occur under concurrent

VR VR schedules because stimulus control is weakened. Why would this not also occur under the concurrent FR FR schedule used by McMillan and Li (1999a)? Perhaps the relation between responses and reinforcers under FR schedules is more discriminable due to its regularity than it is under VR schedules with similar values, thereby resulting in most responses being restricted to the key on which responses have a predictably higher rate of reinforcement. Under the concurrent VR VR schedule, these relations between responding and rates of reinforcer delivery may be less discriminable, thus resulting in probability matching, because under concurrent VR schedules responses can be reinforced after only a few responses or after a large number of responses under both VR schedule components. The merit of these speculations might be questioned by the data from concurrent interval schedules, for which previous studies have shown that graded dose-response curves occur for drug discrimination under both schedules when the rate of reinforcer delivery is variable (concurrent VI VI) and fixed (concurrent FI FI schedules); however, it should be noted that under both of these concurrent FI FI and concurrent VI VI schedules, the rate of reinforcer delivery can be maximized by distributing responses across both keys according to the matching law (Baum, 1979; Herrnstein, 1958). Under these circumstances, whether the interval schedule is fixed or variable is probably less important.

Differences between dose-response curves generated under concurrent VR VR schedules and concurrent FR FR schedules do not appear to be due to differences in baseline performance. The baseline percentages of responding on the pentobarbital-biased key after pentobarbital (98%) and on the saline-biased key after saline (99%) under concurrent VR VR schedules were very close to those obtained under a concurrent FR 10 FR 40 schedule maintaining pentobarbital discrimination (100% and 90%) in the previous study (McMillan & Li, 1999a). Nevertheless, pentobarbital and chlordiazepoxide, which consistently generalized to the training dose of pentobarbital in both studies, produced very different dose-response curves in the two experiments.

Other factors that might influence wheth-

er dose-response curves are graded or quantal under concurrent VR VR schedules include differences among the drugs being tested, individual-animal differences, and differences produced by the response contingencies of the schedules. Each of these factors can be analyzed by summarizing the data in Figures 1 through 4, which show the dose-response curves for drugs under which many or all of the animals made the pentobarbital-biased response. *d*-Amphetamine is not included in this analysis because the pigeons did not meet the criterion for responding on the pentobarbital-biased key after this drug.

If individual pigeons are considered, there are some consistencies. Pigeon 386 always exhibited graded dose-response curves regardless of the drug or schedule. Pigeon 388 was the least likely to respond on the pentobarbital-biased key after drugs other than pentobarbital. After chlordiazepoxide administration, this pigeon met the criterion for responding on the pentobarbital-biased key only under the concurrent VR 10 VR 40 schedule, and did not respond on the pentobarbital-biased key under any of the concurrent schedules after ethanol and phencyclidine. Pigeon 390 was the most likely to show quantal dose-response curves, doing so six of the eight times that responses met the criterion for responding on the pentobarbital-biased key; however, with the exception of Pigeon 386, all pigeons exhibited both quantal and graded dose-response curves under some of these concurrent VR VR schedules. Thus, there are only somewhat consistent individual-animal differences of unknown origin.

It is also possible that the individual schedule parameters could influence the shape of the generalization gradient. It might be anticipated that it would be more difficult to discriminate differences in reinforcement frequency provided by the schedules under the concurrent VR 20 VR 30 schedule than under concurrent VR VR schedules when the differences in response requirements of the two components are larger. For example, there is a much larger difference in the frequency of reinforcement by the schedule components of the concurrent VR 5 VR 50 than occurs under the concurrent VR 20 VR 30 schedule. It might be argued that as the size of one VR

component decreases and that of the other VR component increases, the difference in the size of the VR components would become more apparent and would lead to exclusive responding on the key associated with the higher reinforcement rate. However, these differences in reinforcement frequency did not seem to play a very important role in whether or not quantal or graded dose-response curves were produced, because the size of VR components did not appear to determine the shape of the generalization gradients.

Whether graded or quantal generalization gradients occurred did not seem to depend on the drug. Although pentobarbital was the only training drug studied, whether generalization gradients were being determined for pentobarbital, chlordiazepoxide, or ethanol made little difference in the shape of the curve.

The interpretation of intermediate points on dose-response curves in drug-discrimination experiments has been a problem since the very beginning of the field. Whether these points represent the degree to which a given dose of drug is similar to the dose of drug used as the training dose or represent other phenomena has been argued repeatedly (Colpaert, 1991; Stolerman, 1991). The schedule of reinforcement is a powerful determinant of the shape of the dose-response curve, and either graded or quantal curves can be generated, depending on the schedule of reinforcement. Although a large body of evidence has suggested that interval reinforcement is more likely to generate graded curves and ratio reinforcement is more likely to generate quantal curves, the present experiments complicate such explanations by showing that concurrent VR VR dose-response curves are more likely to be graded than quantal.

Although the schedule of reinforcement seems to be an important determinant of whether the shape of the dose-response curve is quantal or graded, the schedule of reinforcement does not seem to be a major determinant of the position of the dose-response curve on the ordinate (potency of the drug as a discriminative stimulus). A detailed comparison of the potency of discriminative stimuli across different schedules of reinforcement is beyond the scope of this paper,

because the potency of drugs as discriminative stimuli depends on the training dose (Young, Masaki, & Geula, 1992), the species (Picker, 1994), the route of drug administration (Holtzman, Steinfels, & Schmidt, 1994), and other factors. An analysis of drug-discrimination data confined to pigeons with training doses of 4.0 to 5.6 mg/kg pentobarbital is shown in Table 3. The dose required to produce at least 80% responding on the pentobarbital key was used as a measure of generalization to the training dose (a common criterion used to establish schedule control by a drug). Under simple ratio and interval schedules, concurrent schedules, second-order schedules, and tandem schedules, the dose of pentobarbital required to produce generalization hovers about 5.6 mg/kg. This is not unexpected, because the training dose in all of these studies was close to 5.6 mg/kg pentobarbital. When the species, route of drug administration, and the training dose are held constant (relatively), the dose required to produce generalization of the training dose of pentobarbital to other doses of pentobarbital does not seem to change, even when the shape of the dose-response curve is schedule dependent.

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Table 3

Dose of pentobarbital required to produce 80% responding on the pentobarbital key based on mean dose-response curves in various studies in pigeons.

Schedule	Mg/kg to generalize	Reference
Second-order FR 10 FR 5	3.0–5.6	Li and McMillan (1998)
FR 20	3.0–5.6	McMillan, Sun, and Hardwick (1996)
FR 20 (incorrect response resets ratio)	5.6	McMillan, Li, and Hardwick (1997)
FR 30	4.0–5.6	Herling, Valentino, and Winger (1980)
		Jarbe and Ohlin (1979)
FI 90 (s)	3.0–5.6	Kline and Young (1986)
VR 30 (3rd key added for amphetamine)	10.0	McMillan, Li, and Hardwick (2001)
Conc VI 60 VI 240	3.0–5.6	Leberer and Fowler (1977)
Tandem VI 60 FR 10	5.6	Snodgrass and McMillan (1996)
Conc FI 60 FI 240	5.6	Witkin, Carter, and Dykstra (1980)
Conc FI 15 FI 285	3.0–5.6	McMillan, Li, and Hardwick (1997)
Conc FI 100 FI 200	5.6–7.8	McMillan and Li (1999b)
Conc FI 40 FI 80	5.6	McMillan and Li (2000)
Conc FR 10 FR 40	5.6	McMillan and Li (1999a)
Conc VR 20 VR 30	5.6	Current study
Conc VR 10 VR 40	5.6	
Conc VR 5 VR 50	5.6	

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